Author's response to reviews

Title: Long-term outcome of vertebral artery origin stenosis in patients with acute ischemic stroke

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Long-term outcome of vertebral artery origin stenosis in patients with acute ischemic stroke

Editorial requirements:

1. Please include the name of ethics committee in the manuscript.
   : Name of ethics committee was specified in the manuscript
   “This study was approved by the Konkuk University Medical Center Institutional Review Board as a prospective observational study.”

2. Authors’ information:
   Please place the Authors’ Contributions section after Competing interests. Please check the instructions for authors on the journal website for the correct format to use for Authors’ Contributions.
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3. Copy editing:
   After reading through your manuscript, we feel that the quality of written English needs to be improved before the manuscript can be considered further. We advise you to seek the assistance of a fluent English speaking colleague, or to have a professional editing service correct your language. Please ensure that particular attention is paid to the abstract.
   : Proofreading was performed by professional editing service (http://www.aje.com)

Reviewer 1
This is a prospective observational study using a single center registry. The enrolled 774 consecutive patients with acute ischemic stroke and evaluated the clinical significance of VAO stenosis.

Major compulsory revisions>
1. The authors found significant VAO stenosis (> 50%) in 149 patients and 12 of them were treated with intervention and excluded. What was the criteria of angioplasty or stenting in these patients? The impact of exclusion of them should be addressed in Discussion.
   : We added following sentence in discussion: “In our study cohort, the 12 patients who underwent angioplasty and stenting within 1 month after stroke-onset were excluded from our study. A decision for the angioplasty and stenting was based on the individual case-by-case situations: as procedures for acute intra-arterial thrombolysis in 3 patients and concurrent vertebrobasilar and/or carotid atherosclerosis in 9 patients. All of those patients had acute ischemic stroke in the posterior circulation, and they were potentially at high risk for recurrent stroke. Exclusion of those patients from the symptomatic VAO stenosis group might have biased our results. Therefore, type II error may have occurred in our study because of the small number of subjects, very low recurrence rate of posterior circulation ischemic stroke, and the exclusion of some high risk patients.”
2. In patients with symptomatic VAO stenosis, TOAST classification of SAO or CE seems to be irrelevant. If they have significant stenosis and other features compatible with SAO or CE, they should be classified as “Two or more”. However there were 18 SAO and 5 CE patients with symptomatic VAO stenosis in table 1.

Because aim of our study was to investigate the significance of VAO stenosis, VAO stenosis was not considered responsible for the stroke subtype of “large artery atherosclerosis” in this study. We added following sentence in methods section: “Because the aim of our study was to investigate the clinical significance of VAO stenosis, VAO stenosis was not considered as the stenosis responsible for the stroke subtype of large artery atherosclerosis. Stroke subtype in some patients who had symptomatic VAO stenosis was classified as small artery occlusion or cardioembolism instead of two or more causes if they had no other concurrent significant stenosis in the vertebrobasilar system except for VAO stenosis.”

3. The definition of symptomatic VAO stenosis is somewhat confusing. For example, patients with left VAO stenosis and Rt. PICA territory infarction should be classified to have symptomatic VAO according to the author’s criteria.

We agree that VAO stenosis may not be responsible for lesions in the opposite side. We reviewed enrolled patients with symptomatic VAO stenosis and found 8 patients with lesion in the unilateral posterior inferior cerebellar artery (PICA) territory and 2 patients with lesions in the bilateral PICA territories. Among 8 patients with unilateral PICA infarcts, 6 patients had ipsilateral stenosis of VAO and 2 patients had contralateral stenosis of VAO. These 2 patients with infarcts in the contralateral side to VAO stenosis might have had some vascular variations of PICA as cited in reference [19]. Among 2 patients with bilateral PICA infarcts, one had cardioembolic source and the other one was suspicious of cryptogenic embolism. We added following sentence in methods section: “Infarcts in the vascular territory of the posterior inferior cerebellar artery (PICA) and VAO stenosis on the side contralateral to the infarct were also included in the symptomatic VAO stenosis group because PICA branching from basilar artery, anterior inferior cerebellar artery, or contralateral vertebral artery is not a rare variation [19]. However, we could not confirm these variations because we did not perform conventional angiography routinely.”

Reviewer 2

The authors idea is very nice to uncover the "Long-term outcome of vertebral artery origin stenosis in patients with acute ischemic stroke", really being an attractive title. However, some of additional necessary materials should be supplied to obtain a more scientific conclusion. So, the manuscript needs majorly revising. Following are some comments:

1. Comparing outcomes and variates of AIS patients with VAOS to those without VAOS in Stroke registry, especially those without intra-, extra-cranial artery stenosis, may solidify our understanding of VAOS, and obtain a more scientific conclusion.
We compared outcomes and variates of patients enrolled in this study to those of our previously published study used the same stroke registry in a similar period. Patients enrolled in our previous study who had acute lacunar infarct are comparable to AIS patients without intra-, extra-cranial artery stenosis as reviewer suggested. New tables comparing variates and outcomes of our current study and previous study were added as Table 5 and 6. We added following sentence in discussion section: “We compared outcomes and variates of patients enrolled in our study to a previously published study that used the same stroke registry in a similar period [14]. Patients enrolled in the previous study had acute lacunar infarcts and were comparable to acute ischemic stroke patients who did not have intra- or extra-cranial artery stenosis. The baseline characteristics of patients with acute lacunar infarcts were not different from those of VAO stenosis except for age (Table 5). ESRS was slightly higher in the VAO stenosis group, but this increase was not statistically significant. The annual event rates of outcomes were not different (Table 6). Considering the most favorable outcomes were in patients with lacunar infarcts among stroke subtypes [30], outcomes of the VAO stenosis group comparable to those of lacunar infarcts may support a hypothesis that there will be a generally favorable outcome in patients with VAO stenosis.”

2. In this study, the recurrent stroke is a very important outcome index. Please clarify the definitions of ischemic stroke in posterior or anterior circulation and unknown stroke.

Definitions of ischemic stroke in posterior or anterior circulation and unknown stroke were clarified. We added following sentence in methods section: “Whenever available, a brain CT or MRI was obtained at the time of the recurrent neurological events to confirm the type of recurrent stroke. Posterior circulation ischemic stroke was defined as clinical symptoms correlated with new lesions in the brainstem, cerebellum, or occipital lobe in the vascular territory of vertebrobasilar circulation. Anterior circulation ischemic stroke was defined as clinical symptoms correlated with new lesions in the vascular territory of the anterior cerebral artery, middle cerebral artery, or internal carotid artery. Hemorrhagic stroke was defined as either a parenchymal, subarachnoid, or intraventricular hemorrhage detected on a brain CT or MRI that is associated with the recurrent neurological events. In cases where brain imaging could not be obtained by investigators, if recurrent stroke was confirmed by telephone interview, it was classified as unknown stroke.”

3. The definition of symptomatic or asymptomatic VAOS used by authors seems inaccurate, as VAOS resulting in posterior circulation TIA is also viewed as being symptomatic, in addition to posterior circulation ischemic stroke. It may be objective and better to divide VAOS into VAOS with or without acute infarct in posterior circulation.

We agree that symptoms of posterior circulation TIA can be vague, therefore, patients with TIA who had no acute ischemic lesion on DWI were not included in our study. We added following sentence in methods section: “Because symptoms of posterior circulation TIA can be vague, TIA patients who did not
have acute ischemic lesions on DWI were excluded from our study.

Definition of symptomatic or asymptomatic VAO was clarified as VAO stenosis with or without acute infarcts in the posterior circulation: “To relate the clinical significance of VAO stenosis to the vascular territory of the index stroke, patients were classified into an asymptomatic VAO stenosis group when acute infarcts were observed in the anterior circulation (Figure 1A) or into a symptomatic VAO stenosis group when acute infarcts were observed only in the posterior circulation (Figure 1B).”

4. Please be careful in explaining that the long-term outcome of VAOS with acute infarct in posterior circulation is worse than VAOS without acute infarct in posterior circulation, for the former has a higher proportion of co-existing VBA stenosis or occlusion in other sites.

: We agree with reviewer's comment. We added following sentence in results section: “When comparing the asymptomatic and symptomatic VAO stenosis groups, concurrent vertebrobasilar stenosis was more prevalent in patients with symptomatic VAO stenosis (21.9 % in the asymptomatic group vs. 38.4 % in the symptomatic group, p = 0.037) (Table 1).” and in discussion section: “A higher prevalence of concurrent vertebrobasilar stenosis in the symptomatic VAO stenosis group could have contributed to the worse outcome of the posterior circulation ischemic stroke.”

5. ESRS being a predictor of recurrent cardiovascular events should be put into the ABSTRACT.

: We revised the abstract as reviewer suggested. We added following sentence in the results: “In a multivariate analysis, the hazard ratio, per one point increase of the Essen Stroke Risk Score (ESRS) for the composite cardiovascular outcome, was 1.46 (95% CI, 1.02-2.08, p = 0.036).” and in the conclusions: “Additionally, ESRS was a predictor for the composite cardiovascular outcome.”

6. Table 2 does not tell us the conditions of 2 groups. Please add these, as readers usually would like to know whether there is a difference in risk factor management and control between 2 groups.

: Table 2 was revised to compare 2 groups. Table 2 showed that optimal medical treatment was adequate in both groups. There was no difference in the risk factor management between 2 groups. We added following sentence in results section: “Compared to the baseline, follow-up profiles of blood pressure, total cholesterol, LDL cholesterol, and HbA1c were significantly improved in both groups (Table 2). The performance of optimal medical treatment for risk factor management and control was adequate in both groups.”

7. Please revise the CONCLUSION section based on new findings.

: We carefully revised the manuscript based on new findings.